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EXAMINER	
MONTANARI, DAVID A	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/678,723	**Applicant(s)** MARBAN ET AL.
	Examiner David Montanari	**Art Unit** 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2009*.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,20-34,42,46-48 and 77-82* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-4, 6, 20-34, 42, 46-48 and 77-82* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed on 9/4/2009 have been entered.

2. The objection to claims 1, 46 and 47 is withdrawn in view of Applicants amendments to the claims.

3. Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 are examined in the instant application.

4. It is noted that the status identifiers of certain claims are incorrect as presented in the claims filed on 9/4/09. See for example claim 4, which was amended to depend from claim 0 but was listed as previously presented. This however did not preclude examination of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record in the Non-Final office action mailed on 3/5/09, pages 3-9

The rejection is on the grounds that the claims encompass a lethal GEM protein and a variant of the GEM protein which does not regulate calcium channel activity. Further the claims encompass the transduction of naked DNA to control calcium channel activity in 15%-25% of excitable cells.

Response to Arguments

Applicants Arguments

Applicants argue in amendment filed on 9/4/2009 that in contrast to the transduction efficiency of 60% discussed in Example 4, which was lethal to some animals, the 15-25% transduction efficiency is not lethal. Applicants continue that the administration of viruses carrying nucleic acids that encode the WT GEM protein, when transduced at levels of 15-25% result in modulated calcium channel activity, without the lethal effect sometimes observed with higher transduction levels.

Applicants continue to argue that working example 4 demonstrates that the W269G variant attenuates myocyte and organ hypertrophy, ameliorates ventricular dysfunction, and suppresses fibrosis during pathological pressure overload and is non-lethal.

Applicants continue that in light of the amendments to independent claims 1, 47, and 48, the specification provides all necessary structural information and functional characteristics to enable the artisan to practice the methods as claimed without the need for undue experimentation.

Response

While Applicant has amended the claims to recite that either the W269G variant or the full-length amino acid encoded by nucleic acid set forth in SEQ ID NO: 1, such that 15%-25% of the excitable cells are transduced, these amendments do not overcome all aspects of the pending enablement rejection . Applicants in their amendment to the claims have overcome the issues of unpredictability regarding any nucleic acid combinations encoding the GEM protein as set forth on pages 4-5 of the Non-Final mailed on 3/5/2009.

However, there still remains several issues of enablement that render the claimed method unpredictable in practice. The previous Non-Final Action (3/5/09) discussed that in some working examples the W269G mutant is no different from a negative control and exhibits no calcium channel activity modulation (Non-Final, 3/5/09, pg. 5 citing pg. 44 Example 2 lines 18-20). Compounding this fact is that the WT GEM protein when delivered under certain conditions such as a hypertensive phenotype is lethal to the recipient (Non-Final, 3/5/09, pg. 5 citing pg. 46 lines 30-31, Example 4).

The previous Non-Final action (3/5/09, pg. 5) discussed that in the working examples (1-5), the full-length wild-type sequence set forth in SEQ ID NO: 1 that encodes the GEM protein is very potent (when overexpressed) in its ability to reduce intracellular calcium by regulating calcium channel activity. In this regard Applicant has used a “weakened” form of the GEM protein, represented by the W269G mutant, to evaluate the ability of the claimed method to modulate calcium channel activity. Applicant has amended the claims to recite that the full-length protein encoded by SEQ ID NO: 1 will only be transduced in 15%-25% of excitable cells.

However this newly added claim limitation is not enabled by the specification as neither the specification nor the art at the time of filing taught how to transduce only 15%-25% of excitable cells using only a nucleic acid encoding a GEM protein. Not all claims are drawn to adenovirus delivery and claims 1, 46 and 47 encompass naked DNA delivery. The 15%-25% transduction of cells was due to the limitations of adenoviral delivery and thus is a property of adenovirus efficiency based upon the dose administered. The specification does not teach how to transduce only 15%-25% of excitable cells using naked DNA. To obtain 15%-25% transduction of excitable cells, the skilled artisan must first know what amounts and dosage achieve transduction, for example of 50% or 100% of excitable cells. Applicants in their support of this amendment cite the teachings of Murata et al. who noted that adenovirus (encoding GEM protein) only transduced cells at levels of 15%-25% and that this effect was non-lethal. However the teachings of Murata et al. are not sufficient since the method taught by Murata, adenovirus delivery, is not analogous to the naked DNA delivery of independent claims 1, 46 and 47. The art teaches that naked DNA, both delivery and uptake, is unpredictable. For example, Liu et al. (2007, J. Gene Med., Vol. 9, pgs. 613-619) teach that when naked DNA is delivered intravenously up to 50% is taken up by the liver (Abstract, parag. 3) and that even large quantities of naked DNA are rapidly removed from the circulation (pg. 913, last parag.). Liu continues to teach that combination of naked DNA degrading in the blood and its further removal from circulation by the liver are the two major components that are responsible for naked DNA elimination following administration (pg. 617 col. 2 parag. 3).

Thus in view of this teaching in the art, the skilled artisan would find the amended claims further unpredictable in practice. If the majority of naked DNA is rapidly removed from circulation, then the skilled artisan would find the controlled contacting of 15%-25% of excitable cells with the nucleic acid of the claims unpredictable.

Coupled with the unpredictability of the new claim amendments is that the working examples also present conflicting results between the WT GEM and the W269G mutant (Non-Final rejection, pg. 6 last parag. bridge pg. 7 parag. 1). Specifically the specification teaches that the delivery of the WT GEM shortened the QT interval (Example 2, pgs. 44), and caused a reduction of heart rate in atrial fibrillation (Example 3, pg. 45) in guinea-pigs as well as attenuation of cardiac hypertrophy (Example 4, pg. 46) in mice. However, in contrast to the WT GEM, the W269G mutant in this example did not change the QT interval when used under the same conditions. The claims recite that the W269G mutant can be used in addition to the WT GEM protein to modulate the activity of a calcium channel, however the working examples teach that their activities at the calcium channel level are not synonymous and thus the skilled artisan must further study and explore whether the WT GEM or the W269G mutant should be used to modulate a particular calcium channel activity.).

In addition to these issues of unpredictability discussed above the previous Non-Final rejection (pg. 7 parag. 2) also discussed the unpredictability of the claimed method based upon the teachings in the art. For example, Beguin et al. teach that the GTP-bound form of kir/GEM (a Ras-related small G-protein) inhibits high-voltage-activated calcium channel activity by interacting directly with the beta-subunit (pg. 701, Abstract). Beguin continues to teach that inhibition of L-type calcium channels by kir/GEM prevents calcium triggered exocytosis in hormone-secreting cells and propose that kir/GEM interacts with beta-subunits regulating calcium channel expression at the cell surface (pg. 701, Abstract, last four lines). Beguin summarizes that kir/GEM could have a protective effect against an overload of calcium (toxicity) that impairs a variety of cellular functions and may also inhibit cell proliferation by reducing calcium-mediated cell growth (pg. 705, col. 1 parag. 1, last four lines). However, while Beguin teaches that using GEM protein could have a protective effect against an overload of calcium, this protective effect is conditional as the working examples summarized above demonstrate. Using WT/full-length/or fully active GEM protein to modulate calcium channel activity is near total in its effectiveness to blockade calcium channel excitement. Applicants have attempted to balance this by using a mutant of the WT GEM protein that is less-effective and less lethal or a full-length GEM protein that is only transduced into 15-25% of excitable cells. All of this leads the skilled artisan to determine that the claimed method is both undue in practice and unpredictable since the sequence and level of expression of the GEM protein has such a significant impact on the calcium channel modulation in excitable cells to the extent that the sequence may kill the subject or may have no effect at all.

In conclusion, based upon the lack of teaching in the specification regarding the transduction of only 15-25% of excitable cells with a nucleic acid encoding a GEM protein and the disagreement among the working examples and the art over what levels of GEM protein are required to modulate calcium channel activity the skilled artisan could not predictably practice the claimed method. It is important to note that expressing the GEM protein in even 15%-25% of excitable cells is still a form of overexpression which both the working examples and the art teach is unpredictable due to the lethal effects of inhibiting calcium activity in a cell.

Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the Non-Final Action mailed on 3/5/2009.

Response to Arguments

Applicants Arguments

Applicants argue in amendment filed on 9/4/2009 that they have amended independent claims 1, 46 and 47 to recite two forms of GEM protein, the full-length and the W269G variant. Applicants conclude that they were in possession of the two amino acid sequences recited in the amended claims at the time the application was filed.

Response

While Applicant has amended independent claims 1, 46 and 47 to recite that variant is W269G of SEQ ID NO: 1, the claims still encompass additional variants. While in the first instance in the independent claims, the variant is identified as a W269G mutant, the claims recite open language that would encompass additional variants of said mutant. Further claim 22, which ultimately depends from claim 1, recites in line 3 "a sequence encoding the GEM protein or a variant thereof" and thus the claims are open with respect to additional variants and not just the particular W269G mutant. It is agreed that Applicant was in possession of the full-length GEM protein set forth in SEQ ID NO: 1 as well as the W269G variant at the time of filing, however Applicant was not in possession of additional variants of W269G at the time of filing. The previous written description rejection (3/5/09) set forth on pages 9-12 that the Applicant was only in possession of the full-length GEM protein nucleic acid sequence and the W269G variant at the time of filing and that no additional variants are described in the specification to indicate that Applicant was in possession of further W269G variants. The specification has not described any other structural features, other than the nucleic acid sequence set forth in SEQ ID NO: 1 and the particular W269G mutant, that would indicate that Applicant was in possession of additional variants that would modulate the activity of a calcium channel in an excitable cell. The protein encoded by the nucleic acid of SEQ ID NO: 1 must modulate calcium channel activity in an excitable cell and in this regard Applicant has only demonstrated possession of two nucleic acid sequences which code for proteins having said activity. Thus for the reasons of record and above the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 6 and 20-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4, 6 and 20 recite that they depend from claim “0”, however there is no claim 0. Thus said claims are improperly dependent and are rejected on the basis of depending from a cancelled or nonexistent claim. However for purposes of examination in the instant action these claims are interpreted to depend from claim 1 as recited in the previous claim set filed on 12/15/2008.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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